Early Progress at UPMC: When Brain Diseases Affect the Brain-Gut Axis

By Klaus Bielefeldt, MD, PhD

Gastroenterologists are used to hearing about the brain-gut axis, a concept introduced decades ago. Walter Cannon, MD, a pioneer of modern physiology, emphasized nearly one century ago that “great emotional excitement can seriously interfere with the starting of the process or its continuation.” We have since learned more about the importance of early adverse life events, as well as anxiety and depression, in the development and manifestations of functional gastrointestinal disorders, which are among the most common problems physicians encounter in their daily practices.

The importance of neural modulation and control of gut function becomes evident as we approach patients who suffer from neurologic illnesses. Essential daily processes, ranging from swallowing to defecation, are often affected. Clearly, typical treatments appropriate for another patient may not be appropriate for someone with impaired neurologic functions. For example, laxatives may improve constipation but leave a wheelchair-bound patient with the threat of overwhelming urgency or even fecal incontinence.

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Neurogastroenterology: A Developing Subspecialty

The University of Pittsburgh is among the world’s leaders in neuroscience, and is addressing mechanisms of the nervous system, as well as patient perceptions of pain and disability. Over the past decade, the Division of Gastroenterology, Hepatology, and Nutrition has worked with internal colleagues to develop the Center for Pain Research to assemble physicians who are also trained scientists to be pioneers in neurogastroenterology.

This issue of UPMC Digest highlights this GI subspecialty that is critical to patients and research investigations, but remains elusive to our understanding and delivery of effective treatment.

Klaus Bielefeldt, MD, PhD, is leading neurogastroenterology clinical translational efforts. He provides vision, direction, and mentoring to an outstanding working group. Dr. Bielefeldt’s cover article highlights work with co-faculty member David Levinthal, MD, PhD, to address gastrointestinal problems in multiple sclerosis (MS). Dr. Levinthal provides an overview of his specific MS findings on Page 8.

Eva Szigethy, MD, PhD, leads the innovative Visceral Inflammation and Pain (VIP) Center, and addresses the problem of narcotic bowel syndrome (NBS) on Page 4. NBS involves increased abdominal pain in conjunction with increased opiate “analgesia,” and is probably a more common disorder than we, as physicians, realize.

Nausea is a major problem treated by gastroenterologists, but condition mechanisms are poorly understood. Charles Horn, PhD, who co-coordinated an international conference on nausea in Pittsburgh this fall, describes fascinating studies with the musk shrews, with implications for understanding and controlling nausea both in clinical practice and in the context of chemotherapy. Additionally, Kenneth Fasanella, MD, discusses ineffective esophageal motility, a common manometric finding in patients with gastroesophageal reflux disease. Since its initial description by Don Castell, MD, several decades ago, we have learned much more about underlying mechanisms, but little about the need for and effects of treatment.

The mechanisms of neuroinflammation, pathologic neurologic responses, and pain syndromes in pancreatitis, pancreatic cancer, inflammatory bowel disease, and liver diseases are also being evaluated by our Division. These exciting discoveries will be highlighted in future issues of UPMC Digest.

Finally, training the next generation of leaders remains a priority of the Division, and an interesting patient case on Intraductal Papillary Mucinous Neoplasm is presented by GI fellow, Matthew Warndorf, MD, on Page 6.

Please enjoy this issue — and remember to get your CME credit for all that you learn!

David C. Whitcomb, MD, PhD
Giant Eagle Foundation Professor of Cancer Genetics
Professor of Medicine, Cell Biology and Physiology, and Human Genetics
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Ineffective Esophageal Motility Disorder: The Goose Is Cooked

By Kenneth E. Fasanella, MD

In this issue of *Digest*, we are focusing on neurogastroenterology. When asked to contribute an article, I thought to myself, “What do I, as an endosonographer and Barrett’s specialist, have to contribute to such a topic?” Then I thought about the entities that have a dominating effect on my clinic days, and tend to frustrate many gastroenterologists.

Refractory GERD, noncardiac chest pain, chronic cough, globus sensation, functional dysphagia, and laryngopharyngeal reflux all tend to fit under the umbrella of nonspecific esophageal motility disorders (NEMD), for which few, if any, effective treatments are available. However, relatively recent research, including new technology such as multichannel intraluminal impedance testing and high-resolution manometry, has begun to shed some light on the interplay between these symptoms and NEMD, particularly related to ineffective esophageal motility (IEM).

The term IEM was introduced by Donald Castell, MD, in 1997 to describe a substantial subset of NEMD patients for whom at least 30 percent of swallows failed to meet an effective contraction amplitude of 30 mmHg. Studies in Dr. Castell’s laboratory demonstrated that this subset of patients had significantly delayed esophageal acid clearance, leading to prolonged acid exposures similar to patients with systemic sclerosis when recumbent.™ IEM is found in 20 to 50 percent of GERD patients. Two studies have shown a linear relationship of increasing prevalence of IEM from GERD to increasing grades of erosive esophagitis. In patients with more atypical manifestations, prevalence of IEM is significantly higher in those with chronic cough and positive symptom associated probability (SAP) compared to chronic cough patients without positive SAP. Another study analyzed patients with globus sensation who were resistant to PPI. Among this subset, almost 50 percent had abnormal motility, two-thirds of whom had IEM. In general, IEM is much more prevalent in patients with GERD-associated respiratory symptoms than in patients with typical GERD. This is likely associated with acid clearance times, which are approximately doubled.

IEM is among the most commonly diagnosed conditions in patients sent for motility testing, but this diagnosis is also one of the most difficult to treat. There is no clear response to surgery, such as with achalasia. Some small studies, which investigate outcomes of fundoplication in this IEM group...
Narcotics for the Bowel: Hazards Can Outweigh Benefits

By Eva M. Szigethy, MD, PhD

According to the Centers for Disease Control and Prevention (CDC), prescription opiate use is the fastest-growing problem in the United States. While short-term narcotics prescribed for postsurgical pain by licensed providers may play a role in this issue, there is a growing concern in the field that the hazards of longer-term prescribed opiates for abdominal pain may outweigh the benefits.

Adults with Crohn’s disease who were prescribed narcotic analgesics had an increased risk of serious infections and death compared to Crohn’s patients not on these agents. Additionally, narcotics are given to more than 70 percent of hospitalized patients with inflammatory bowel disease (IBD), even though identifiers such as duration of IBD, prior psychiatric diagnoses, outpatient narcotic use, irritable bowel syndrome, and prior IBD-specific surgery are all risk factors for narcotic use. Grunkemeier, et al. defined a category of central hyperalgesia producing abdominal pain that, in combination with high-dose or chronic opiates, results in narcotic bowel syndrome (NBS). NBS is characterized by chronic or frequently relapsing abdominal pain that worsens with continued or escalating doses of narcotics. NBS can occur in any patient who is prescribed opiates, not only those with IBD.

Opiates also affect GI motility through associated symptoms such as constipation, nausea, bloating, and discomfort. There are two probable processes involved in side effects from opiates. Opioid bowel dysfunction or opiate-induced constipation involves activation of mu receptors, which leads to motility disturbances in the gut, while NBS is more linked to the activation of central nervous system, producing hyperalgesia. The exact neurobiological mechanisms underlying the paradoxical increase in abdominal pain in NBS, even with escalating doses of opiates, are unknown. However, glial cell activation leading to dorsal horn release of cytokines that upregulate pain transmission, bimodal opioid modulation (both excitatory and inhibitory) in the spinal cord, and secondary release of anti-opioid modulators, such as dynorphin and cholecystokinin, has been postulated. At the behavioral systems level, an acrimonious patient-doctor interaction has been reported when patients have greater levels of pain, despite the use of narcotics. This frustrates the patient and leads to increased health care utilization. In turn, exasperated physicians continue to prescribe the narcotics. This vicious circle can be interrupted, but the only effective treatment involves a diagnosis of NBS and the initiation of an opiate withdrawal program.
As abdominal pain in NBS increases, eating can be restricted due to delayed gastric emptying and ileus. Abdominal scans may show signs of partial intestinal obstructions in NBS, but these are often caused by pseudo-obstructions and fecal retention. The NBS hallmark symptom is worsening pain despite the escalation of narcotic dosages.

Non-narcotic treatment strategies for NBS have been developed and have shown efficacy for reducing abdominal pain, at least in short-term cases. A biopsychosocial approach anchored by a solid doctor-patient relationship is critical for success. This effective communication needs to be combined with a consistent plan for narcotic withdrawal and non-opiate treatments to manage presenting complaints, such as bowel symptoms, pain, and emotional distress (such as anxiety or depression). Building from an empathic therapeutic alliance, the rationale and benefits for stopping narcotics must be explained. During this precontemplation stage, it is important to utilize positive motivational techniques and process resistance thoughtfully, all while teaching cognitive behavioral coping strategies. Non-narcotic medications for pain need to be individualized, but may include serotonin noradrenergic reuptake inhibitors (SNRIs), tricyclic antidepressants, or even mood stabilizers. Additionally, medications such as clonidine and benzodiazepines may help with withdrawal. Any narcotic withdrawal plan needs to be firm, and is often best achieved with a brief inpatient medical hospitalization. After successful detoxification, continued follow-up therapy is essential, since patients are at an especially high risk for relapsing to narcotic use six months after detoxification.

The Visceral Inflammation and Pain (VIP) Center in the Division of Gastroenterology, Hepatology, and Nutrition has developed a protocol to help patients with NBS safely detox from narcotics in collaboration with medical professionals who developed this approach. The protocol is strongly based on the solid implementation of effective alternative strategies to cope with the pain. In an era of individualized comprehensive medical care that improves patient quality of life while also being cost-effective, targeting NBS is an important area for reducing GI-related morbidity and mortality.

Dr. Szigethy is an associate professor of medicine and psychiatry with the Division of Gastroenterology, Hepatology, and Nutrition. She serves as the medical director of the Division’s Visceral Inflammation and Pain (VIP) Center.

References:
Intraductal Papillary Mucinous Neoplasm Causing Recurrent Acute Pancreatitis, Necrotizing Pancreatitis, and Multifocal Adenocarcinoma

By Matthew G. Warndorf, MD
Gastroenterology Fellow

A 58-year-old woman presented for evaluation after a third episode of acute pancreatitis (AP) of unclear etiology. During previous hospitalizations, common etiologies such as alcohol, hypercalcemia, and hypertriglyceridemia had been excluded. Endoscopic ultrasound (EUS) revealed gallbladder sludge and a small cystic lesion (1.0 x 0.7 cm) in the uncinate process of the pancreas consistent with side branch intraductal papillary mucinous neoplasm (IPMN). A laparoscopic cholecystectomy was performed in case biliary microlithiasis was the cause of her recurrent acute pancreatitis (RAP).

Fifteen months later, she developed a fourth episode of acute pancreatitis. A repeat MRI showed stable size of IPMN (Figure 1). Approximately five months later, she presented with her fifth RAP episode, which was complicated by necrotizing pancreatitis involving most of the body of the pancreas. She required prolonged pancreatic rest with nasojejunal tube feeding and, ultimately, endoscopic cystgastrostomy for walled-off pancreatic necrosis (Figure 2). Surveillance MRI 16 months later showed an increase in the size of the IPMN to 2.7 x 1.5 x 3.0 cm with a region of T1 hypointensity without corresponding T2 hyperintensity of questionable etiology. Follow-up EUS described a complex cystic structure containing hyperechoic material concerning for mural nodule. Fine needle aspiration on EUS showed a CEA of 132 ng/mL with no malignant cells.

After a thorough discussion of management options, she underwent a total pancreatectomy. Pathology revealed an IPMN with high-grade dysplasia and invasive moderately differentiated adenocarcinoma, measuring 0.5 cm in greatest dimension in the pancreatic head, as well as a 0.4 cm focus of moderately differentiated adenocarcinoma in the distal pancreas.

This case highlights IPMN’s wide clinical spectrum. In this case, IPMN presented with RAP, which led to
Nausea: Neuro-Signaling From the Upper GI Tract

By Charles C. Horn, PhD

Nausea acts as an early warning system to help us avoid food toxins that could make us sick. These warning signals can produce a learned food aversion — a Pavlovian conditioned response. Nausea also may be triggered by GI diseases or medications, such as cytotoxic chemotherapy, inhalational anesthesia, and opioid analgesics. Chronic nausea can be debilitating in patients suffering from gastroparesis, cyclic vomiting syndrome, and hyperemesis gravidarum (a severe form of “morning” sickness).

Nausea and vomiting, key focal points of my research, were discussed during Biology and Control of Nausea and Vomiting 2013, a recent conference held at the University of Pittsburgh this past autumn (InternationalVomitingConference.org). This symposium attracted a scientifically diverse audience, from as far away as Australia. Meeting sessions focused on personalized medicine and genetics, gastroparesis and cyclic vomiting syndrome, vestibular and GI integration, assessment and control of nausea, and cellular biology. This two-day event ended in an open session to discuss major research problems, with a debate on two critical dilemmas:

• How to determine the biological substrates of nausea.
• The use of animal models to accomplish this goal.

As discussed at this conference, a better understanding of the relationship between nausea and vomiting is central to forward progress, and a key solution is to use a biological model that represents both processes. Evidence indicates that the same stimuli drive both nausea and vomiting, with low levels of stimulation producing nausea and higher levels (beyond a threshold) triggering the emetic reflex. For GI diseases, this signal appears to be conveyed by the vagus nerve. “Vagus” is a medieval Latin term that translates to “wandering,” and the vagus, with its lengthy path and numerous innervations, certainly seems to wander throughout the body. Vagal afferent neurons supply information to the hindbrain from multiple levels of the GI tract. Our lab recently demonstrated that diverse rodent species lack a vomiting reflex. Using an isolated brainstem, we showed that electrical stimulation of the vagus produced the unique pattern of neuromotor outputs of emesis in musk shrews, but not in rodents. Emesis is a key measure of the specific activation of the nausea-to-emesis continuum, and the lack of a rodent motor circuit for vomiting makes it difficult to translate rodent physiology to human responses.

We use musk shrews in my lab at the University of Pittsburgh Cancer Institute to investigate the neural circuits that produce nausea signaling from the GI tract. This mouse-sized animal helps us to broadly test hypotheses using a complete set of behavioral, anatomical, and electrophysiological methods commonly employed in ubiquitous mouse and rat experiments. My lab is working to define the pattern of nausea-related signals from GI vagal afferent fibers utilizing high-throughput electrophysiological approaches and recording neural activity through mathematical analysis. Key goals are to understand the relationship between mechanical and chemical activation of these afferent fibers, and to determine the role of intrinsic GI circuits — the enteric nervous system — in these responses. Moving forward, we want to uncover the pharmacologic underpinnings of these signals. Ultimately, this focus will provide insight into novel therapeutic approaches to control difficult-to-treat nausea in patients.

Dr. Horn is an associate professor of medicine and anesthesiology with the Division of Gastroenterology, Hepatology, and Nutrition.

References:

Gastrointestinal Symptoms and Syndromes in Multiple Sclerosis

By David J. Levinthal, MD, PhD

The complex and integrated functions of the gastrointestinal system are subject to control by peripheral nerves that innervate the GI tract. These nerves are ultimately regulated by a central neural network distributed across multiple sites within the brain and the spinal cord. Thus, neurologic illnesses that impact either the peripheral or central nervous system can lead to significant gastrointestinal dysfunction. At the Center for Neurogastroenterology at UPMC, we provide a coordinated approach among UPMC’s neurology and gastroenterology teams to care for patients suffering from gastrointestinal symptoms of neurologic origin. This collaborative approach enhances patient care and serves as a ready platform for clinical research studies aimed at advancing the understanding of these associations and improving treatment options and outcomes.

Multiple sclerosis (MS) is a progressive, demyelinating disease of the central nervous system that often leads to significant physical, cognitive, and emotional problems. MS is a relatively common disorder that affects up to 400,000 patients in the United States alone. Historically, the clinical evaluation and management goals for MS patients focused on treating skeletal muscle detriments that impacted mobility. However, over the past two decades, there has been an increasing awareness that MS is also associated with other physical symptoms, such as those related to impairments of urinary and GI systems.

Previously, the GI problems thought to be most common in MS patients involved impaired deglutition and defecation, processes which require coordinated skeletal muscle activity. The diagnostic and clinical approaches to MS care have changed dramatically over the past 10 years due to the early introduction of new disease-modifying therapies. However, little is known about the prevalence and nature of GI symptoms in MS patients within this new clinical context. Furthermore, MS may be associated with other GI problems that are not linked with deteriorating skeletal muscle function. To address these gaps in knowledge, our research team sought to define the prevalence of GI symptoms and syndromes in a large sample of contemporary MS patients.

We recruited 218 patients with known MS from the Center for Neuroimmunology at UPMC. Each patient completed a standardized questionnaire that assessed the severity of MS and specific GI symptoms,
as well as a comprehensive survey of gastrointestinal symptoms (the Adult Functional GI Disorders Rome III Questionnaire). We found that nearly two-thirds (65.6%) of the MS study patients indicated experiences of at least one persistent GI symptom over the previous six months. The most commonly reported GI symptom was constipation (36.6%), and both dysphagia and fecal incontinence were prevalent. Surprisingly, nearly 30% of these patients reported dyspepsia, a constellation of symptoms unlikely to be mediated by impairments of skeletal muscle coordination (Figure 1A). Based on validated diagnostic algorithms, patients met criteria for functional dysphagia (14.7%), functional dyspepsia (16.5%), functional constipation (31.7%), and irritable bowel syndrome (19.3%) (Figure 1B). Further analysis showed that functional dysphagia, dyspepsia, and irritable bowel syndrome were all significantly more common in MS patients with self-identified mood disorders.

These findings have implications for the management of MS patients, since GI problems can significantly impair quality of life and may interfere with MS treatments. Interestingly, we also discovered a relationship between reported mood disorders and some of the GI problems observed in MS patients. While this latter association warrants further study, it also suggests potential diagnostic approaches and therapeutic targets for this population. Given the prevalence of many GI symptoms in MS patients, screening for such symptoms should be incorporated into routine patient assessments.

Dr. Levinthal is an assistant professor of medicine with the Division of Gastroenterology, Hepatology, and Nutrition. His clinical practice and research interests focus on the neural regulation of the gastrointestinal tract and functional bowel disorders. Dr. Levinthal is also a recent recipient of a National Institutes of Health K Award, “Cerebral Cortical Influences on the Stomach,” and he will study novel brain-based therapies for patients with refractory functional gastrointestinal disorders.

Reference:
Brain-Gut Axis continued from Page 1

The prolific intersection between neurologic and gastrointestinal illnesses has become an enhanced focus for our UPMC Neurogastroenterology Group since David Levinthal, MD, PhD, joined our faculty (see more about Dr. Levinthal’s research on Page 8 of this issue). In the laboratory, Dr. Levinthal and our team work to unravel the complex brain network that regulates autonomic function, and recent studies that underline the critical importance of a fully operational brain-gut axis. Upon examination of a large sample of patients with multiple sclerosis, about two-thirds of the participants endorsed at least one gastrointestinal problem, with defecation disorders and dyspeptic symptoms among the most common. These associated changes in sensory and motor function not only contribute to the development of these gastrointestinal problems, but also make them more complex. For example, up to 50 percent of patients with constipation also experience episodes of fecal incontinence. How can we help them to avoid being caught between this proverbial rock and a hard place? Another group, patients with movement disorders, exhibit even more complex challenges. In these patients, the prokinetics used by gastroenterologists to bring the gut to life also shut down the patients’ voluntary motor control systems. We are eager to continue to care for these patients and learn more about their puzzling symptoms.

UPMC’s close collaboration between the seemingly divergent fields of neurology and gastroenterology has created a unique niche in neurogastroenterology that integrates interests and expertise to tailor care to the special needs of affected individuals.

Dr. Bielefeldt is an associate professor of medicine with the Division of Gastroenterology, Hepatology, and Nutrition. He directs the Neurogastroenterology and Motility Center within the Division, and his research interests concentrate on pain and functional bowel disease.

Reference:

Intraductal Papillary Mucinous Neoplasm continued from Page 6

necrotizing pancreatitis and subsequent development of multifocal synchronous cancer. IPMN incidence is rising rapidly, likely from the increasing use of imaging studies.1 IPMNs are known to cause AP due to blockages of the pancreatic ducts by mucinous secretions, which lead to elevated ductal pressure and premature release of pancreatic enzymes.2 In a retrospective surgical study, at least one episode of AP was seen in 34.6% (64/185) of patients with IPMN. Of these patients, 62% (40/65) had two to five AP episodes, and 6% (4/65) had six to 10 AP episodes prior to IPMN resection.3 The risk of malignancy in side branch IPMN (overall 25.5%, invasive 17.7%) is less than that for main duct IPMNs (overall 61.6%, invasive 43.1%).4 According to international guidelines, resection of an IPMN is indicated in the presence of obstructive jaundice, a cyst of greater than 3 cm, presence of a mural nodule, presence of features suspicious for main duct involvement, and cytology suspicious or positive for malignancy.5 This case highlights the association of IPMN with RAP, as well as the importance of regular surveillance of IPMN due to potential transformation into malignancy.

References:
Ineffective Esophageal Motility Disorder

compared to patients with GERD and normal motility, have been published. While results demonstrate similar outcomes and some normalization of motility parameters postoperatively, most study series have short, six-month outcome time frames, raising doubt about conclusion longevity.8

Few effective medical therapies have been documented. Topical bethanecol has been investigated in a pilot study and has been a noted treatment in published abstract form. Some improvement in the percentage of peristaltic swallows at a 5 mg dose were demonstrated, but this study failed to show a dose-response relationship, and was very small, evaluating only five subjects.9 Oral bethanecol has demonstrated some improvement as well, but use tends to be limited due to its cholinergic side-effect profile. Another study examined the effectiveness of buspirone, a 5-HT₃ receptor agonist that has been shown to modulate gastroduodenal motor function. Buspirone demonstrated significant increases in mean distal esophageal wave amplitude and duration, as well as mean LES resting and residual pressures in healthy volunteers. However, this study has not been replicated in patients with IEM, so it is too early to conclude that a therapeutic benefit exists in this patient population.

In conclusion, IEM is a very common esophageal motility disorder with an unknown etiology. Patients with refractory and atypical manifestations of GERD commonly have this condition complicating their disease. While IEM may improve with antireflux surgery, surgical outcome data is not convincing. Well-tolerated and effective medical therapies are still under investigation. Until an appropriate medication is discovered, those of us who treat this disease will unfortunately continue to be frustrated with anecdotal, unproven, off-label treatment options.

Dr. Fasanella is an assistant professor of medicine with the Division of Gastroenterology, Hepatology, and Nutrition, and serves as the Division’s program director for the Gastroenterology Fellowship Program.

References:

Pittsburgh Gut Club Programs for 2014

The Pittsburgh Gut Club is a regional forum for gastroenterologists and related medical professionals. All of the Pittsburgh Gut Club physician education programs will be held at The University Club, located on the University of Pittsburgh campus. Gut Club membership is $150 for the entire series and includes accreditation, a networking reception, dinner, and the lectures. While designed for gastroenterologists, this educational series is appropriate for all medical professionals. For more information, please contact Joy at joj2@pitt.edu. The 2014 Gut Club season will feature the following internationally recognized speakers:

### April 10

**Treatment of C. Difficile: From Flagyl to Fecal Microbiota Transplant**

**Colleen R. Kelly, MD**  
Clinical Assistant Professor of Medicine  
Brown University  
Providence, R.I.

### April 24

**Barrett’s Esophagus: When to Burn, When to Wait...**  
**John M. Inadomi, MD**  
Cyrus E. Rubin Endowed Chair in Medicine  
Professor of Medicine  
Head, Division of Gastroenterology  
University of Washington School of Medicine  
Seattle, Wash.

### May 8

**Women’s Health in the Clinical Course and Treatment of IBD**  
**Sunanda V. Kane, MD, MSPH**  
Professor of Medicine  
Department of Gastroenterology and Hepatology  
Mayo Clinic  
Rochester, Minn.